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Anti-Cytokine Strategies beyond Anti-Tumour Necrosis Factor-α Therapy: Pathophysiology and Clinical Implications

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Key Words
Inflammatory bowel disease · Pathophysiology · Environmental factors · Hygiene hypothesis

Abstract
Cytokines are small proteins produced by a broad range of cells important in cell signaling. They include interleukins, but also chemokines, interferons, and tumor necrosis factors (TNF). They play an important role for communication between cells of the innate and adaptive immune system. The cytokine network is complex and, therefore, therapeutic interventions are difficult. The first anti-cytokine strategy successfully introduced into IBD therapy was the neutralization of TNF by antibodies. Beyond targeting this cytokine anti-IL-23 strategies were demonstrated to be of therapeutic benefit in IBD. Anti-IL-6 strategies seem to have clinical potential but also cause some risk for the patient due to the lack of CRP increase upon severe inflammation. JAK inhibitors target the intracellular signaling of several cytokine receptors and represent a promising class of broader and somewhat unspecific anti-cytokine strategies. Many other anti-cytokine approaches have failed due to the redundant nature of the cytokine network. Whether further anti-cytokines strategies have potential for IBD treatment may be evaluated in future studies.
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Introduction

Around the millennium, anti-tumour necrosis factor (TNF)-α antibodies have been introduced into the therapy first to treat Crohn's disease (CD) [1–8] and later on to treat ulcerative colitis (UC) [9–13]. They have significantly changed the therapeutic landscape for inflammatory bowel diseases (IBD) patients [14, 15].

TNF has been shown to be one of the most pathophysiological relevant pro-inflammatory factors for the pathophysiology of IBD [16–20]. Neutralization of TNF has beneficial effects in a large number of patients [15, 21, 22]. Nevertheless, there is a need for additional therapeutic options due to a non-negligible fraction of patients with primary non-response, loss of response or side-effects.

As we have shown recently in the Swiss IBD Cohort Study, surgery is still frequent in CD patients and even after 30 years, up to 80% of the patients are likely to undergo surgery [23, 24]. The question is whether this trend changed significantly in the era of the anti-TNF antibodies. A recent study presented by Jeuring et al. [26] from the Netherlands on a Dutch population-based cohort study in the south Limburg area [25] came to a disappointing result. The disease behavior of CD patients diagnosed in the biological era was not different to that diagnosed in the pre-biological era [26]. CD patients

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diagnosed in the pre-biological and biological era shared a similar risk of developing structuring or penetrating disease [26]. These findings indicate that the disease phenotype and the development of the disease phenotype have not changed significantly despite changes in the CD management.

Data from the same cohort, on the other hand, showed that the number of surgeries done for just inflammatory complications has significantly decreased. This indicates that with anti-TNF antibodies we can successfully treat inflammation and all problems directly associated with inflammation. However, the processes finally leading to the penetrating and stricturing complications of the disease may be completely different. Perhaps these processes are not mainly mediated by TNF and may subsequently require different treatment options [27, 28]. The disappointing fact is that bowel damage cannot be prevented with anti-TNF therapy and this clearly indicates a need for the development of further therapies beyond current strategies.

New Treatment Targets: Lessons from IBD Pathogenesis

We generally assume that there is an uncontrolled immune reaction to endogenous and exogenous factors triggered by genetic predisposition [29–32]. A barrier defect is frequently seen as the first pathophysiological relevant problem [33, 34]. This barrier defect may be caused by a reduction of phosphatidylcholine incorporation into the mucus layer of the mucosa [35–37]. Stremmel et al. [37] have shown that the mucus layer in UC patients is decreased in thickness [38]. This has stimulated new developments for a phosphatidylcholine substitution therapy as a new therapeutic approach in UC [39–42]. So far, there is no biological therapy that can address this problem.

Among the known alterations in the barrier functions of IBD also are the differences with respect to defense in secretion as shown by the studies of Stange and Wehkamp [43--49]. The authors have attributed CD as being mainly a 'defensin-deficiency' [49] and in the case of ileal CD, it is referred to as Paneth disease (with Paneth cells being the origin of secreted α-defensin) [50]. Defensins certainly play a role in the barrier function of the mucosa. The differences shown for IBD patients and controls are intriguing. However, it is unclear whether the differences in defensin expression and secretion are a primary defect or a secondary response to the presence of inflammation.

In addition to the barrier defect in active IBD, there are endogenous and exogenous factors that may aggravate the local inflammation such as food antigens, the intestinal microbiota or environmental factors such as nanoparticles or food additives [51]. Those aggravating factors that act on an already present barrier defect may be more relevant in a genetically predisposed individual [52–54].

Genetic susceptibility has been shown to occur in genes responsible for the barrier function and also in innate immunity genes and in adaptive immunity genes [52–54]. Endogenous and exogenous factors acting on a barrier defect and innate immune defect associated with a genetic pre-disposition lead to a deregulated immune response and finally to intestinal inflammation. This means that biological therapies that mainly focus on the deregulated immune response address their target at a relatively late stage in the pathophysiological cascade that finally leads to IBD.

Nevertheless, cytokines are attractive targets for biological approaches in IBD therapy. Neurath [55] has summarized in a very nice overview article in Nature Reviews and Immunology in 2014 the cytokines that have been shown to be relevant in IBD. Important macrophage-derived cytokines are interleukin (IL)-12, IL-6, IL-23 and TNF. They act on the activation and regulation of the adaptive immune system, mainly T-cells. Important T-cell derived cytokines are interferon-γ, IL-17, IL-22 and also IL-6 and TNF [55]. Th2 cell–derived cytokines are for example IL-5 and IL-13 [55]. Cytokines secreted by regulatory T-cells are for example IL-10 and transforming growth factor β. Evidently, cytokines that are derived from regulatory T-cells should not be antagonized, as they are anti-inflammatory by nature. In contrast, these cytokines may represent promising approaches for therapeutic substitution [55].

The Promise of Precision Medicine

With the call for 'precision medicine', doctors try to promise that in course of time we will know which patient will benefit from which therapy [56–58]. Indeed many of our IBD patients complain that they are subject to a doctor-driven 'try and error approach'. In a typical moderate-to-severe IBD patient, we may first start with immunosuppression and if this does not work within a few weeks or months, we take the next step towards administering anti-TNF therapy. If anti-TNF therapy is not successful, we may use anti-integrin strategy. If this strategy is also not successful, then we may take the next step of applying new anti-cytokines strategies.

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Precision medicine promises now that each patient should benefit from the first therapy used after a respective diagnostic approach. It is claimed that DNA tests taken before the onset of a therapy will identify the target population that benefits in all cases from a tailored therapy [57, 58]. This indeed is a nice promise. However, in IBD it seems to be rather unrealistic. It is more and more clear – as indicated by Rappaport [59] in recent paper in PLoS One – that genetic factors are not major causes of chronic diseases. Therefore, a simple genetic test will not identify the patients that benefit most from a specific therapy. In addition, the cytokine network is extremely complex [60]. Recent manuscripts show that there are multiple backup mechanisms for every cytokine and in fact – at least for the time being – it is hard if not virtually impossible to predict which target in whom may be most promising [61, 62].

The current pipeline in adult IBD therapy is rich in product developments. In 2013, we had the pleasure to write a review on new anti-cytokines for IBD 'What is in the pipeline?' [63]. Unfortunately, 2/3 of the anti-cytokines strategies that were in the pipeline at that time have failed and are no longer followed. However, there are several lines of development that currently seem to be quite promising.

Anti IL-23 Strategies in IBD

Sandborn et al. [64, 65] reported phase II trials of Ustekinumab in patients with moderate to severe CD. A total of 526 patients who had failed anti-TNF treatment were enrolled into the study to receive either placebo or Ustekinumab in a dosage of 1, 3 or 6 mg/kg i.v. [64]. The prior endpoint of the study was the clinical response at week 6 [64]. One hundred thirty-one patients who received placebo were compared to about the same number that received the different Ustekinumab preparations. With respect to the clinical response at week 6, there was a significant difference as compared to placebo for all concentrations used [64]. The clinical response at week 8 was highest for the 6 mg/kg dosage [64]. Remission at week 6, however, showed no significant difference between the treatment groups and placebo. As Ustekinumab has been approved as Stelara® for the treatment for psoriasis, there was a small GETAID study published by Wils et al. [66] from Lille about the efficacy and safety of subcutaneous Ustekinumab in refractory CD patients. This was a multicenter retrospective study on off-label use of Ustekinumab in patients with desperate situations [66]. One hundred thirty-five patients were recruited. Thirteen patients were excluded, as the follow-up was less than 3 months. Finally, 122 were included in the analysis. Out of those 122 patients, 79 patients (64.7%) had a clinical benefit at 3 months [66]. Forty-three patients had a clear non-response at 3 months. Out of the 79 patients with a clinical benefit at 3 months, the majority had luminal CD [66]. Only a minority had perianal disease. However, out of 12 patients with perianal CD, 8 showed a clinical benefit [66].

Clinical response at week 6 was also the primary endpoint in the phase 3 Uniti-2 trial that most likely will lead to the approval of Ustekinumab for CD [67]. At 6 weeks, the clinical response with placebo was 28%. In contrast, there was a clinical response of 51.7% with 130 mg subcutaneously and a clinical response of 55.5% in the 6 mg/kg i.v. group [67], keeping in mind that the 6 mg/kg i.v. group also was the highest dosage group in the phase II trial that was reported earlier. After 8 weeks, the placebo response was 32%, the response with the subcutaneous preparation was 47%, and with the i.v. preparation, it even increased to 58% [67]. The subcutaneous preparation dosage that is used for psoriasis is 45 mg. Therefore, it appears that the dosage needed to be effective in IBD and CD is much higher as compared to psoriasis.

Is this treatment strategy effective only for Ustekinumab or are there other drugs that target the same cytokine? IL-23 is a heterodimer of 2 proteins. Ustekinumab is directed against the p40 subunit in IL-23 that is also is present in IL-12. The second protein subunit that is in contrast to p40 specific for IL-23 is the p19 unit. Targeting IL-12 has been shown not to be successful in IBD. Therefore, it was considered that targeting the p19 subunit of IL-23 might be a more specific and promising approach. In a randomized double blind placebo controlled phase II induction study of MEDI2070, patients with active CD were dosed with anti-p19 antibody, if they had previously failed anti-TNF therapy. Sands et al. [68] have found that targeting anti-IL-23 might be successful in general and this is not restricted to anti-p40 antibodies. Targeting IL-23 alone and not IL-12 may offer a better benefit risk profile as compared with the dual inhibition of IL-12 and IL-23 by an anti-p40 antibody [68]. When Sands et al. [68] looked into the clinical efficacy in week 8 with the intention of treating population, they found that the difference with respect to CDA100 response between placebo and the antibody was 22.5%. The placebo response was 26.7%, whereas the drug response was 49.2%. With respect to complete remission defined as a CD activity index (CDAI) below 150 at week 8, the placebo response

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was 15% and the treatment response was 27.1%, thereby making up a difference of 12.2%, which was not statistically and significantly different with respect to composite endpoints [68]. For the composite CDAI response, there was at week 8 a difference of 32.4%, which was highly significant; the placebo composite response was 10%, whereas the drug response was 42.4% [68]. Also with respect to the CDAI remission composite, there was a difference of 15.4% [68]. The placebo response was 8.3% and the drug response was 23.7%. This indicates that in general anti-IL-23 therapies provide a successful therapeutic strategy. We will in the near future see anti-IL-23 therapies introduced into the treatment strategy for CD.

Anti-IL-6 Therapy

The biology of IL-6 is even more as complex as the biology of anti-IL-12 or anti-IL-23. IL-6 binds to 2 proteins to induce responses of cells. It has a specific receptor. However, the IL-6 receptor will only induce signal transduction when a second protein called gp130 is present according to the molecular weight. After binding of IL-6 to the IL-6 receptor, a complex with 2 molecules of gp130 is formed that finally mediates signal transduction [69, 70]. Cells that harbor only gp130 (which can also be a co-receptor for other cytokine receptors) are not responsive to IL-6 (such as epithelial cells and smooth muscle cells) [71–74]. On the other hand, hepatocytes and some leukocytes express both proteins and respond well to the cytokine [71–74].

It needs to be emphasized that the expression of IL-6 receptor in hepatocytes is essential for the formation of C-reactive protein (CRP). When IL-6 is neutralized, no stimulation of CRP production is found. There could even be severe inflammation; however, it is not indicated by increases in CRP.

In 2004, in Gastroenterology, Ito et al. [75] reported a pilot trial of tocilizumab, an anti-IL-6 antibody, in CD patients. A total of 36 patients with a CDAI higher than 150 were randomized to receive either placebo or alternating infusions of 8 mg/kg tocilizumab and placebo every 2 weeks or tocilizumab 8 mg/kg every 2 weeks [75]. The response and remission rate were evaluated at week 12. The tocilizumab infusion every 2 weeks showed a clinical response in 75% of the patients [75]. Clinical remission was seen only in the tocilizumab groups [75]. This has stimulated a number of developments with different anti-IL-6 antibodies. A development by BMS has finally been stopped during the phase II trial, as a number of bowel perforations were observed. Unfortunately, those patients showed up in emergency situations, but the severity of the complications was not realized because they did not develop sufficient CRP levels.

Pfizer has supported the ANDANTE trial. Patients could have been previously treated with anti-TNF; they were supposed to have a CDI greater than 220 but less than 450 and CRP levels above 5 mg/l [76]. A colonoscopy had to confirm the ulcerations. The patients received 3 dosings of the anti-IL-6 antibody or placebo. One group received 10 mg subcutaneously, one received 50 mg and one received 200 mg subcutaneously. The 200 mg group stopped receiving the anti-IL-6 antibody or placebo after observing bowel perforations in another trial, which was not part of the CD trial. The patients were followed up for 28 weeks. The primary endpoint was a decrease of CDAI of 70 points or CDAI remission. At week 12, both groups were statistically significant for the 50 mg dose [76]. There was a placebo response of 29.1% and a response of 38.3% with the 10 mg group ($p = 0.19$) and 47.6% with the 50 mg group ($p = 0.045$). With respect to CDAI remission, 11.5% achieved remission in the placebo group, 15% ($p = 0.33$) achieved remission in the 10 mg group and 28.5% ($p = 0.004$) achieved remission in the 50 mg group. These results are quite encouraging [76]. However, at the moment it seems to be unclear whether the anti-IL-6 program will be maintained due to the risk of bowel perforation.

JAK Inhibitors

Many cytokines signal to the cells via intracellular proteins, the so-called Janus kinases or JAKs [77]. There are mainly 3 JAKs and one similar protein called Tyk2 and they associate with different receptors. For example, the IL-6 receptor associates with JAK1, Tyk2 and JAK2. On the other hand, the IL-12 and IL-23 receptors associate with JAK2 and Tyk2 alone, whereas JAK1 does not play a role [77]. For the IL-2 receptor, signaling via JAK1 and JAK3 has been shown. Different JAK inhibitors target different JAK proteins. Ruloxitinib, Lestaurtinib, Tofacitinib and others target JAK1 and also JAK2. Tofacitinib also inhibits JAK3 [77]. For Tofacitinib, an inhibition of JAK 3 and less JAK1 and even less JAK2 have been shown.

Tofacitinib has been tested in patients with UC [78]. A total of 194 patients with active UC (Mayo score >6) received either placebo or Tofacitinib in a dosage of 0.5, 3, 10 or 15 mg twice daily [78]. The primary endpoint in the study that was reported by Sandborn et al. [78] in the New England Journal of Medicine in 2012 was the clinical re-

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sponse with a decrease of the Mayo score of 3 points or 30% at week 8. Tofacitinib at the dosage of 15 mg showed a significant effect with respect to clinical response. With respect to clinical remission, which was just 10% in the placebo patients but 33%, 48 or 41%, respectively, in the Tofacitinib groups 3, 10 and 15 mg of Tofacitinib showed significant effects [78]. With respect to endoscopic response, again the highest concentration was found to the most effective and it showed a significant result [78]. For endoscopic remission, again all 3 higher concentrations were effective; however, it has to be kept in mind that in this phase 2 trial, numbers were still small.

A larger trial now has confirmed the beneficial data for UC; however, in CD, the effect of Tofacitinib was not statistically significant (unpublished, presented at DDW 2015). In contrast, Filgotinib, a selective JAK1 inhibitor that revealed to be effective in rheumatoid arthritis with a planned phase 3 program in this indication, was shown to be effective in a phase II study in patients with moderate to severe CD [79]. Filgotinib subsequently is the first JAK inhibitor to show efficacy in CD. The 48% clinical remission rate was statistically significant versus placebo after 10 weeks of induction therapy [79]. The placebo response was that only 23% of patients received a CDI lower than 150 points. Also, for the clinical response which was at a CDI decrease of 100 points or more, there was a difference between placebo (41%) as the Filgotinib 200 mg group achieved a clinical response of 60% ($p = 0.0386$) [79]. There also was a significant improvement in clinical response as well as in the IBD quality-of-life questionnaire. The Filgotinib safety profile was similar to what has been described previously for other JAK inhibitors [79].

Summary

In this review, we outlined that the cytokine network is very complex and multiple backup mechanisms exist. This explains why many trials with biologicals that targeted specific cytokines have failed in the past. However, 6 biologicals are currently approved for the treatment of IBD: 4 anti-TNF agents (infliximab and biosimilars, adalimumab, golimumab and certolizumab pegol) and 2 anti-integrin agents (natalizumab and vedolizumab; natalizumab only in the United States and not in Europe)

Beyond anti-TNFs (and anti-integrins), IL-23 strategies will soon be approved and will be available, especially for anti-TNF non-responders and refractory patients. Anti-IL-6 strategies do have clinical potential but also risks due to the lack of CRP increase and the reported bowel perforations. At the current moment, it remains doubtful whether additional drug-development programs of this therapeutic principal in IBD will be further advanced. JAK inhibitors target several cytokine receptors and represent a promising class of broader and somewhat unspecific anti-cytokine strategies. They will also likely be soon available for the treatment of IBD patients (presumably with Tofacitinib as first-in-class available agent for UC).

Whether further anti-cytokines strategies will have a potential for clinical practice will be elucidated in the future.

Disclosure Statement

Gerhard Rogler has consulted to Abbot, Abbvie, Augurix, Boehringer, Calypso, FALK, Ferring, Fisher, Genentech, Essex/MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions and Zeller; Gerhard Rogler has received speaker's honoraria from Astra Zeneca, Abbott, Abbvie, FALK, MSD, Phadia, Tillots, UCB, and Vifor; Gerhard Rogler has received educational grants and research grants from Abbot, Abbvie, Ardeypharm, Augurix, Calypso, Essex/MSD, FALK, Flamentera, Novartis, Roche, Takeda, Tillots, UCB and Zeller.

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